Fostering Translation of Genetic Research on Common Disease: An NIDDK Perspective

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Encouraging successes from research on Mendelian genetic diseases

The canonical genetic translation path:

Gene discovery → **Functional characterization** → **Novel therapeutics**

Gene discovery → **Diagnostics**

Over 1700 ‘gene tests’ currently available

Translation of genome findings in complex disease is still much more challenging

Hard to find the specific base change(s) responsible for the effect

Changes may alter gene regulation of adjacent or distant genes

Gene discovery → **Functional characterization** → **Novel therapeutics**

Effect of any specific variant is small

Diagnostics

Most genetic findings in complex diseases are not clinically useful

Genes have been discovered for major complex genetic diseases within the NIDDK portfolio

Crohn's Disease: Over 30 genes identified

But : 10% of the overall variance in disease risk, which may be as much as a fifth of the genetic risk

Barrett et al., Nature Genetics 40, 955 - 962 (2008)

Type 2 diabetes: 20 or more genes identified

But: while the sibling relative risk for type 2 diabetes is 3, having all known risk variants would only account for a sibling relative risk of 1.07

Lango et al, Diabetes. 2008 Nov;57(11):3129-35 (2008)

Obesity: 17 genes implicated

But: account for less than 1% of the total genetic variation

Hofker & Wijmenga; Nature Genetics 41, 139-140 (2009)

End stage renal disease: Only one replicated major effect gene; appears to behave more like a Mendelian trait (MYH9)

Freedman et al, Kidney Int. 2009 Apr;75(7):736-45. (2009)

If there is no clear relationship between variants and gene products, what are the next steps in translation?

- Nurture the basics
- Promote sharing of data and resources
- Build resources to last through ‘generations’ of rapidly evolving methods
- Pursue the science at every stage – seize current opportunities

Nurture the basics

NIDDK supports major consortia to identify genes and carry out replication studies for:

type 1 diabetes, type 2 diabetes, end-stage renal disease and diabetic kidney disease, chronic kidney disease, Inflammatory Bowel Disease, and others

Numerous smaller grants to identify genes for other diseases, and develop novel analytic methods

Complex traits involve multiple genes and environmental factors.

NIDDK is spending hundreds of millions of dollars for research on the molecules, pathways and systems causing disease.

Data sharing is a key part of a translation agenda

- Open Access
- Rapid deposition of sequence data in GenBank
- Required sharing of data and unique resources, and the use of minimally restricted licensing terms for sharing
- Data-sharing plans for large applications (> $500K/yr)
- Sharing plans for applications proposing to create transgenic animals

Create resources to facilitate translation research in the future: Major clinical cohorts –with rich phenotypic data and samples

A2ALL - Adult to adult living donor liver transplantation cohort

AALF - Adult Acute Liver Failure Network

BARC - Biliary Atresia Research Consortium

CKiD - Pediatric chronic renal insufficiency study

CRIC - Chronic Renal Insufficiency Cohort Study

CRISP - Consortium for Radiological Imaging Studies of PKD

DAC - Dialysis Access Consortium

DILIN - Drug Induced Liver Injury Network

DPP - Diabetes Prevention Program

DPT-1 - Diabetes Prevention Type 1 Trial

EDIC/DCCT - Epidemiology of diabetes interventions and complications/diabetes control and complications trial Family Study

FAVORIT - Folic Acid for Vascular Outcome Reduction in Transplantation Trial

FBEC - Familial Barrett's Esophagus Consortium

FHN - Frequent Hemodialysis Network

FSGS/FONT - Focal Segmental Glomerulosclerosis Trial

HALT PKD - The Polycystic Kidney Disease Treatment Network

IBD - Inflammatory Bowel Disease Genetics Consortium

ICdb - Interstitial Cystitis Database

ICCTG RCT#1 - Interstitial Cystitis Trial Group

LABS - Longitudinal Assessment of Bariatric Surgery

LTD - Liver Transplantation Database and Follow-up

MaGIC - Maryland Genetics of Interstitial Cystitis

MDRD - The Modification of Diet in Renal Disease

MTOPS - The Medical Therapy of Prostatic Symptoms

NANS - National Analgesic Nephropathy Study

NASH - Nonalcoholic Steatohepatitis Study

PALF - Pediatric Acute Liver Failure Network

PEDS-C - Pegylated Interferon +/- Ribavirin for Children with Hepatitis C

SIGT - The Screening for Impaired Glucose Tolerance Study

T1DGC - Type 1 Diabetes Genetics Consortium

TEDDY - The Environmental Determinants of Diabetes of the Young

TrialNet - Type 1 Diabetes Clinical Trial Network

Virahep-C - Study of Resistance to Antiviral Therapy of Chronic Hepatitis C

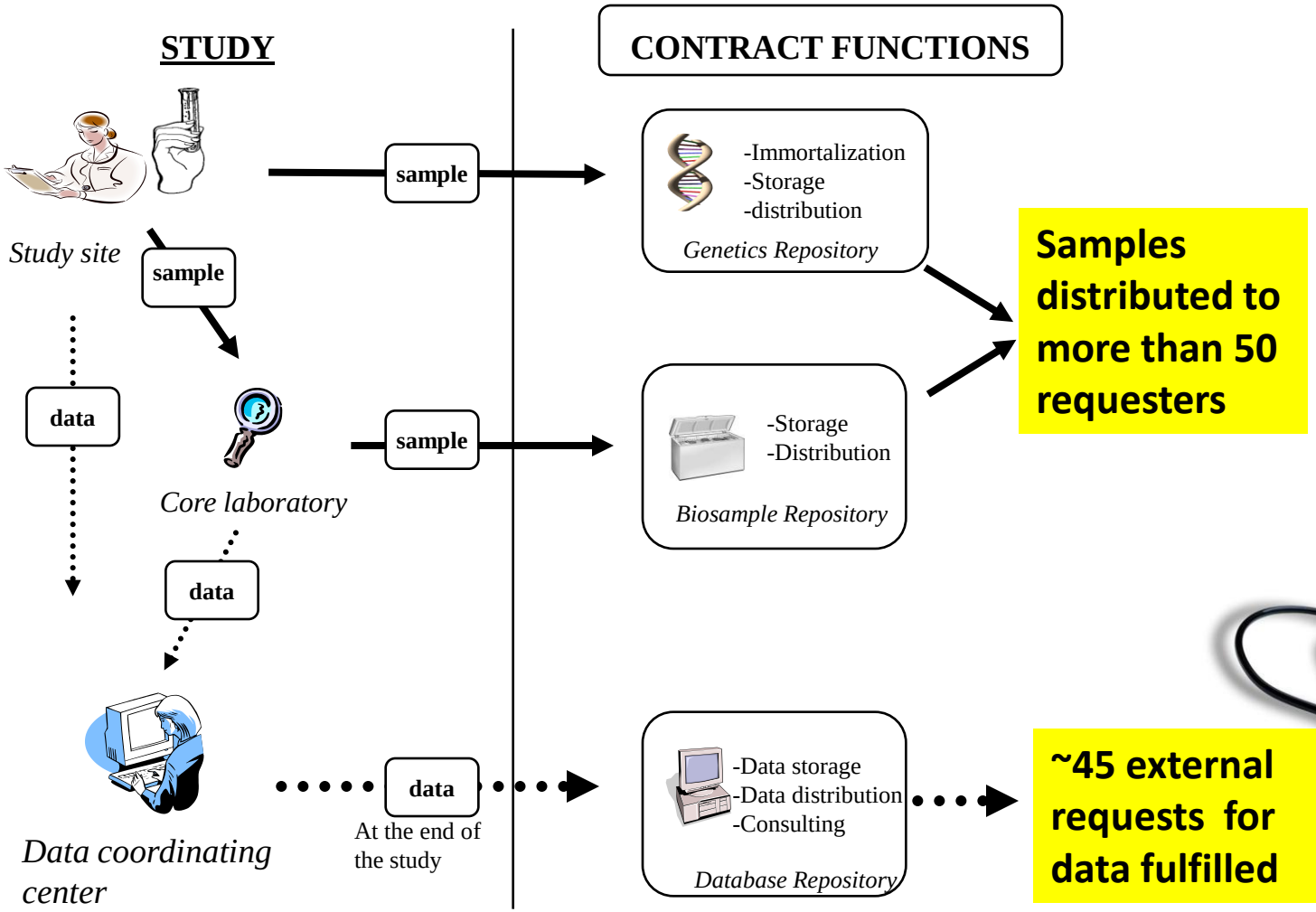
Create resources to facilitate translation research in the future: Data and sample repositories

The NIDDK Central Repositories collect, store and distribute data and samples from major NIDDK-funded clinical studies:

- allow additional studies on characterized samples, enhancing the value of each study
- ensure uniform storage conditions
- simplify access by other scientists to samples
- cost effective, economy of scale in processing genetic samples
- maintain databases after the study's Data Coordinating Center closes

NIDDK Central Repository

The NIDDK Central Repositories:



Translation is a key part of the GEI project

GEI initiatives
Discovery through GWAS
Replication/fine mapping
Sequencing
Functional studies

Bench ⟷ **Bedside** ⟷ **Public**

GEI Translational Research Initiatives

Translation moves discoveries into health practice

What kind of translation is possible now? The GEI Translation initiative

Only the earliest stages of research are ready:

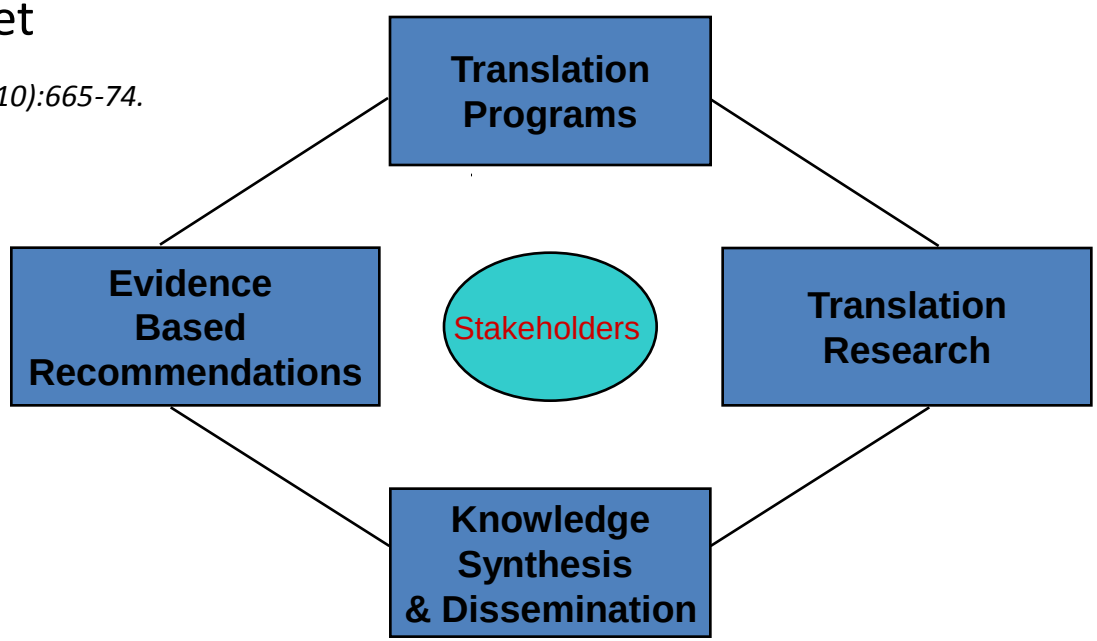
- new diagnostic or other risk factor algorithms that incorporate genetic data
- pilot interventional studies using genetic testing
- pilot research on clinical modification of environmental factors known to interact with specific genes variants
- cost effectiveness studies
- research on patient or provider education regarding genetic findings or clinical outcomes of genetic testing
- research on patient or provider perceptions of environmental or other risk factors that may have specific interactions with gene variants
- assessments of responses to use of personal genetic information in clinical care and disease prevention.

The initiative will spend ~$8-9M over the next two years.

Translation for the future

- NIDDK has joined GAPP Net

Khoury MJ, et al., Genet Med. 2007 Oct;9(10):665-74.

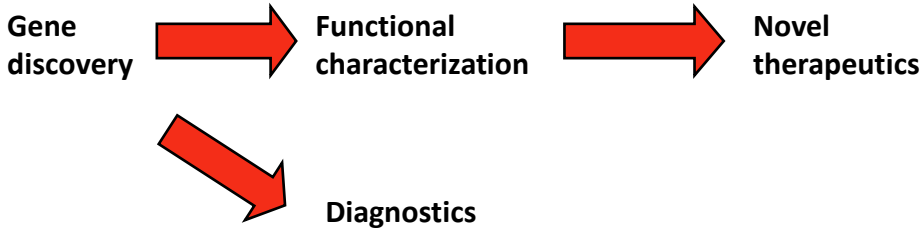


- Future initiatives, pilot studies---> full studies

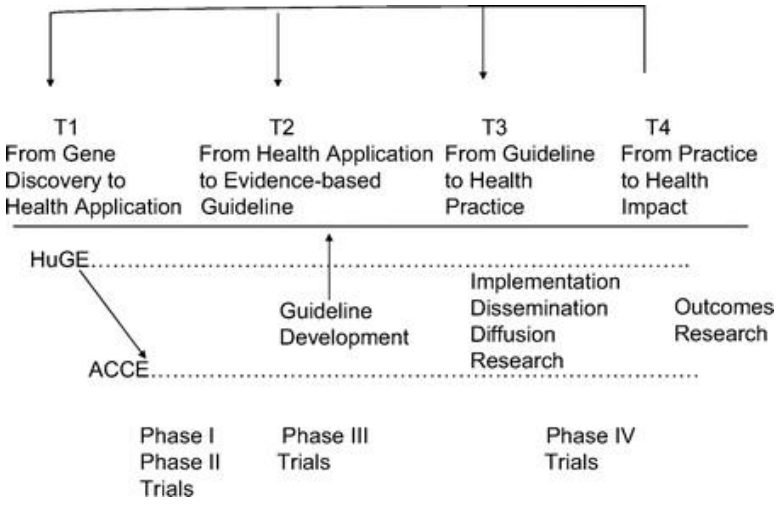
- Poised to take advantage of new opportunities with existing cohorts and resources or new studies

Stages of translation

Where we are:



Where we want to be:



Conclusions

NIDDK's major investments in genetics have yielded many translatable and translated findings for Mendelian disease, complex genetic diseases have been more difficult to study

Personalized medicine based on genetics will require significantly more basic research on genetics

Through a strategy of investment in basic research, data sharing and resource creation, NIDDK is laying the groundwork for future translation